Complete Summary

GUIDELINE TITLE

Infectious Diseases Society of America practice guidelines for clinical assessment, treatment and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis.

BIBLIOGRAPHIC SOURCE(S)

Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, Krause PJ, Bakken JS, Strle F, Stanek G, Bockenstedt L, Fish D, Dumler JS, Nadelman RB. Infectious Diseases Society of America practice guidelines for clinical assessment, treatment and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis. Alexandria (VA): Infectious Diseases Society of America; 2006 Jun 27. 150 p. [381 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Wormser GP, Nadelman RB, Dattwyler RJ, Dennis DT, Shapiro ED, Steere AC, Rush TJ, Rahn DW, Coyle PK, Persing DH, Fish D, Luft BJ. Practice guidelines for the treatment of Lyme disease. Clin Infect Dis 2000 Jul;31(Suppl 1):1-14.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- June 15, 2005, Non-steroidal anti-inflammatory drugs (NSAIDs): The U.S. Food and Drug Administration (FDA) requested that sponsors of all NSAIDs make labeling changes to their products. FDA recommended proposed labeling for both the prescription and OTC NSAIDs and a medication guide for the entire class of prescription products.
- April 7, 2005, NSAIDs: Revised labeling to include more specific information about potential gastrointestinal (GI) and cardiovascular (CV) risks, and information to assist consumers in the safe use of the drugs.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Lyme disease
- Human granulocytic anaplasmosis (HGA) (formerly known as human granulocytic ehrlichiosis)
- Babesiosis

GUIDELINE CATEGORY

Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Dermatology
Family Practice
Infectious Diseases
Internal Medicine
Neurology
Obstetrics and Gynecology
Ophthalmology
Otolaryngology
Pediatrics
Rheumatology

INTENDED USERS

Allied Health Personnel
Physicians

GUIDELINE OBJECTIVE(S)

- To provide clinicians and other health care practitioners with recommendations for the management of patients in the United States with

suspected or established Lyme disease, human granulocytic anaplasmosis (HGA, formerly known as human granulocytic ehrlichiosis), or babesiosis
- To provide recommendations for prevention of these infections, all of which may be transmitted by certain species of Ixodes ticks

TARGET POPULATION

Patients with suspected or established Lyme disease, human granulocytic anaplasmosis, or babesiosis

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention

1. Avoidance of tick-infested areas
2. Use of protective clothing
3. Inspection of entire body to locate and remove ticks
4. Tick and insect repellents
5. Single-dose doxycycline prophylaxis after tick bite in special cases

Evaluation

1. Recognition of clinical manifestations and complications of early and late Lyme disease, human granulocytic anaplasmosis, and babesiosis
2. Diagnostic tests for Lyme disease
3. Lumbar puncture and examination of cerebrospinal fluid in patients with suspected central nervous involvement of Lyme disease
4. Examination of synovial fluid when arthritis or joint swelling is present
5. Recognition of symptoms of post-Lyme disease syndrome
6. Diagnostic tests for human granulocytic anaplasmosis and babesial infection, including blood smear evaluation, polymerase chain reaction (PCR), and serology

Treatment/Management

Lyme Disease

1. Oral antibiotics including doxycycline, amoxicillin, and cefuroxime axetil (macrolides, including azithromycin, erythromycin, or clarithromycin only in patients who cannot take doxycycline, amoxicillin, or cefuroxime axetil)
2. Parenteral antibiotics including ceftriaxone, cefotaxime, and penicillin G for Lyme Disease with neurologic involvement, severe heart involvement, and selected cases of Lyme arthritis
3. Hospitalization, monitoring, and temporary pacemaker for Lyme carditis
4. Symptomatic therapy for antibiotic-refractory Lyme arthritis, including nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections of corticosteroids, and disease-modifying anti-rheumatic drugs such as hydroxychloroquine
5. Consultation with cardiologist or rheumatologist, as necessary

Human Granulocytic Anaplasmosis

1. Doxycycline
2. Rifampin

Babesiosis

1. Combination of atovaquone plus azithromycin
2. Combination of clindamycin plus quinine
3. Partial or complete red blood cell exchange transfusion as indicated

MAJOR OUTCOMES CONSIDERED

- Incidence and persistence of Borrelia burgdorferi infection
- Incidence of Lyme disease, human granulocytic anaplasmosis, and babesiosis
- Morbidity of disease
- Efficacy of antibiotic chemoprophylaxis and treatment regimens
- Resolution of symptoms
- Adverse effects of antimicrobial therapy
- Quality of life
- Cost effectiveness of antimicrobial therapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline panel performed an extensive review of all of the randomised controlled trials and open-label trials published in peer-reviewed English language journals.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Categories for Quality of Evidence on which Recommendations are Made

I. Evidence from at least one properly randomized, controlled trial
II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results of uncontrolled experiments

III. Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendation

A. Strongly in favor
B. Moderately in favor
C. Optional
D. Moderately against
E. Strongly against

COST ANALYSIS

Tick Bites and Prophylaxis

One cost-effectiveness analysis concluded that a 2-week course of doxycycline is indicated when the probability of infection with Borrelia burgdorferi after a tick bite is $\geq$3.6% and should be considered when the theoretical probability ranges from 1% to 3.5%. Some experts disagree with key assumptions in the model (many of which tended to favor the use of antimicrobial prophylaxis) and consider the duration of treatment to be excessive. However, the findings do argue against routine prophylaxis of all Ixodes scapularis tick bites, since the frequency of Lyme disease was less than 3.6% among placebo recipients in each of the four reported chemoprophylaxis trials.

Late Lyme Disease

In a cost-effectiveness analysis, intravenous (IV) therapy was found to be no more cost-effective than oral therapy for patients with Lyme arthritis; IV therapy was more likely to result in serious complications and was substantially more expensive. Therefore, the authors concluded that oral antibiotics are to be preferred in the initial treatment of Lyme arthritis in the absence of concomitant neurological involvement.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Each recommendation includes a ranking for the strength and the quality of evidence supporting it. Definitions of the levels of evidence (I-III) and grades of recommendation (A-E) are repeated at the end of the Major Recommendations field.

Note: See Tables 3 and 4 of the original guideline document for recommended antimicrobial regimens for the treatment of Lyme disease in adults and children.

Tick Bites and Prophylaxis of Lyme Disease

The best currently available method for preventing infection with Borrelia burgdorferi and other Ixodes species-transmitted pathogens is to avoid exposure to vector ticks. If exposure to I. scapularis or I. pacificus ticks is unavoidable, measures recommended to reduce the risk of infection include the use of both protective clothing and tick repellents, checking the entire body for ticks daily, and prompt removal of attached ticks before transmission of these microorganisms can occur (B-III).

For prevention of Lyme disease after a recognized tick bite, routine use of antimicrobial prophylaxis or serologic testing is not recommended (E-III). A single dose of doxycycline may be offered to adult patients (200 mg dose) and to children ≥8 years of age (4 mg/kg up to a maximum dose of 200 mg) (B-I) when all of the following circumstances exist: a) the attached tick can be reliably identified as an adult or nymphal I. scapularis tick that is estimated to have been attached for ≥ 36 hours based on the degree of engorgement of the tick with blood or on certainty about the time of exposure to the tick; b) prophylaxis can be started within 72 hours of the time that the tick was removed; c) ecologic information indicates that the local rate of infection of these ticks with B. burgdorferi is ≥20%; and d) doxycycline is not contraindicated. The time limit of 72 hours is suggested because of the absence of data on the efficacy of chemoprophylaxis for tick bites following tick removal after longer time intervals. Infection of ≥20% of ticks with B. burgdorferi generally occurs in parts of New England, in parts of the Middle Atlantic States, and in parts of Minnesota and Wisconsin, but not in most other locations in the United States. Whether use of antibiotic prophylaxis after a tick bite will reduce the incidence of human granulocytic anaplasmosis (HGA) or babesiosis is unknown.

Doxycycline is relatively contraindicated in pregnant women and children <8 years old. The panel does not believe that amoxicillin should be substituted for doxycycline in persons for whom doxycycline prophylaxis is contraindicated because of the absence of data on an effective short-course regimen for

prophylaxis, the likely need for a multi-day regimen (and its associated adverse effects), the excellent efficacy of antibiotic treatment of Lyme disease if infection were to develop, and the extremely low risk that a person with a recognized bite will develop a serious complication of Lyme disease (D-III).

Prophylaxis after I. pacificus bites is generally not necessary because infection rates with B. burgdorferi in these ticks are low in almost the entire region in which the tick is endemic. However, if a higher infection rate were documented in specific local areas ($\geq$20%), prophylaxis with single-dose doxycycline would be justified if the other criteria mentioned above are met.

In order to prescribe antibiotic prophylaxis selectively to prevent Lyme disease, health care practitioners in endemic areas should learn to identify I. scapularis ticks, including its stages (see Figure 1 in the original guideline document), and to differentiate ticks which are at least partially engorged with blood (see Figures 2 A and B in the original guideline document) (A-III). Testing of ticks for tick-borne infectious agents is not recommended, except in research studies (D-II).

Health care practitioners, particularly those in endemic areas, should become familiar with the clinical manifestations and recommended practices for diagnosing and treating Lyme disease, HGA, and babesiosis (A-III). Persons who have removed attached ticks from themselves (including those who have received antibiotic prophylaxis) should be monitored closely for signs and symptoms of tick-borne diseases for up to 30 days and in particular for the development of an expanding skin lesion at the site of the tick bite (erythema migrans) that may suggest Lyme disease. Persons who develop a skin lesion or viral infection-like illness within a month after removing an attached tick should promptly seek medical attention to assess the possibility of having acquired a tick-borne infection. HGA and babesiosis should be included in the differential diagnosis of patients who develop fever after an Ixodes tick bite in an area endemic for these infections (A-II). A history of having received the previously licensed recombinant outer surface protein A (OspA) Lyme disease vaccine preparation should not alter the above recommendations. The same can be said for having had a prior episode of early Lyme disease.

Early Lyme Disease

Erythema Migrans

Doxycycline (100 mg twice daily), amoxicillin (500 mg three times daily), or cefuroxime axetil (500 mg twice daily) for 14 days (range 10 to 21 days for doxycycline and 14 to 21 days for amoxicillin or cefuroxime axetil) is recommended for treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic manifestations (see below) or advanced atrioventricular heart block (A-I). Each of these antimicrobial agents has been shown to be highly effective in the treatment of erythema migrans and associated symptoms in prospective studies. Doxycycline has the advantage of being effective for treatment of HGA (but not for babesiosis), which may occur simultaneously with early Lyme disease. Doxycycline is relatively contraindicated during pregnancy or lactation, and in children <8 years of age. Antibiotics recommended for children are amoxicillin (50 mg/kg per day in three divided doses [maximum of 500 mg

per dose]), cefuroxime axetil (30 mg/kg per day in two divided doses [maximum of 500 mg per dose]), or doxycycline if ≥8 years of age (4 mg/kg per day in two divided doses [maximum of 100 mg per dose]) (A-II).

Macrolide antibiotics are not recommended as first-line therapy for early Lyme disease because those macrolides that have been compared with other antimicrobials in clinical trials have been found to be less effective (E-I). When used, they should be reserved for patients who are intolerant of, or should not take, amoxicillin, doxycycline, and cefuroxime axetil. For adults with these limitations, recommended dosage regimens of macrolide antibiotics are azithromycin 500 mg orally daily for 7 to 10 days, clarithromycin 500 mg orally twice daily for 14 to 21 days (if not pregnant), or erythromycin 500 mg orally four times per day for 14 to 21 days. The recommended dosages of these agents for children are azithromycin 10 mg/kg daily (maximum of 500 mg per day); clarithromycin 7.5 mg/kg twice daily (maximum of 500 mg per dose); erythromycin 12.5 mg/kg four times daily (maximum of 500 mg per dose). Patients treated with macrolides should be closely followed to ensure resolution of the clinical manifestations.

First generation cephalosporins such as cephalexin are ineffective for treatment of Lyme disease and should not be used (E-II). When erythema migrans cannot be reliably distinguished from community-acquired bacterial cellulitis, a reasonable approach is to treat with either cefuroxime axetil or amoxicillin-clavulanic acid (dosage of amoxicillin-clavulanic acid for adults: 500 mg three times daily; dosage for children: 50 mg/kg per day in three divided doses [maximum of 500 mg per dose]), since these antimicrobials are generally effective against both types of infection (A-III).

Ceftriaxone, while effective, is not superior to oral agents and is more likely than the recommended orally administered antimicrobials to cause serious adverse effects. Therefore, ceftriaxone is not recommended for treatment of patients with early Lyme disease in the absence of neurologic involvement or advanced atrioventricular heart block (E-I).

Lyme Meningitis and Other Manifestations of Early Neurologic Lyme Disease

The use of ceftriaxone (2 g once daily intravenously [IV] for 14 days [range 10 to 28 days]) in early Lyme disease is recommended for adult patients with acute neurologic disease manifested by meningitis or radiculopathy (B-I). Parenteral therapy with cefotaxime (2 g IV every 8 h) or penicillin G (18 to 24 million units daily for patients with normal renal function, divided into doses given every 4 h), may be a satisfactory alternative (B-I). For patients who are intolerant of beta-lactam antibiotics, increasing evidence indicates that doxycycline 200-400 mg per day in two divided doses orally for 10 to 28 days may be adequate (B-I). Doxycycline is well absorbed orally and thus IV administration should only rarely be needed.

For children, ceftriaxone (50 to 75 mg/kg/day in a single daily IV dose (maximum, 2 g) (B-I) is recommended. An alternative is cefotaxime (150 to 200 mg/kg/day) divided into 3 or 4 IV doses per day (maximum, 6 g/day) (B-II) or penicillin G (200,000 to 400,000 units/kg/day; maximum, 18 to 24 million units/day) divided

into doses given IV every 4 h for those with normal renal function (B-I). Children ≥ 8 years of age have also been successfully treated with oral doxycycline at a dose of 4 mg/kg/day in two divided doses (maximum 100 mg per dose) (B-II).

Although antibiotic treatment may not hasten the resolution of seventh cranial nerve palsy associated with B. burgdorferi infection, antibiotics should be given to prevent further sequelae (A-II). Cranial nerve palsies in patients with Lyme disease are often associated with a lymphocytic cerebrospinal fluid (CSF) pleocytosis, with or without symptoms of meningitis. Panel members differed in their approach to the neurologic evaluation of patients with Lyme disease-associated seventh cranial nerve palsy. Some perform a CSF examination on all such patients. Others do not because of the good clinical response with orally administered antibiotics (even in the presence of a CSF pleocytosis) and the absence of evidence of recurrent central nervous system (CNS) disease in these patients. There was agreement that lumbar puncture is indicated for those in whom there is strong clinical suspicion of CNS involvement (e.g., severe or prolonged headache or nuchal rigidity). Patients with normal CSF examinations and those in whom CSF examination is deemed unnecessary because of lack of clinical signs of meningitis, may be treated with a 14 day course (range 14 to 21 days) of the same antibiotics used for patients with erythema migrans (see above) (B-III). Those with both clinical and laboratory evidence of CNS involvement should be treated with regimens effective for Lyme meningitis as described above (B-III).

Lyme Carditis

Patients with atrioventricular (AV) heart block and/or myopericarditis associated with early Lyme disease may be treated with either oral or parenteral antibiotic therapy for 14 days (range 14 to 21 days). Hospitalization and continuous monitoring are advisable for symptomatic patients, such as those with syncope, dyspnea, or chest pain. It is also recommended for patients with second or third degree AV block, as well as for those with first degree heart block when the PR interval is prolonged to ≤30 msec, because the degree of block may fluctuate and worsen very rapidly in such patients.

A parenteral antibiotic such as ceftriaxone is recommended as initial treatment of hospitalized patients (see recommendations for treatment of Lyme meningitis above) (B-III). For patients with advanced heart block a temporary pacemaker may be required; expert consultation with a cardiologist is recommended. The pacemaker may be discontinued when the advanced heart block has resolved. An oral antibiotic regimen should be used for completion of therapy and for out-patients, as is used for patients with erythema migrans without carditis (see above) (B-III).

Borrelial Lymphocytoma

Available data indicate that borrelial lymphocytoma may be treated with the same treatment regimens used to treat patients with erythema migrans (see above) (B-II).

Pregnancy

Pregnant and lactating patients may be treated in a fashion identical to non-pregnant patients with the same disease manifestation, except that doxycycline should be avoided (B-III).

Late Lyme Disease

Lyme Arthritis

Lyme arthritis can usually be treated successfully with antimicrobial agents administered orally. Doxycycline (100 mg twice daily) (B-I), amoxicillin (500 mg three times daily) (B-I) or cefuroxime axetil (500 mg twice daily) (B-III) for 28 days, is recommended for adult patients without clinical evidence of neurologic disease. For children, amoxicillin (50 mg/kg/day in three divided doses [maximum of 500 mg per dose]) (B-I), cefuroxime axetil (30 mg/kg/day in two divided doses [maximum of 500 mg per dose]) (B-III), or doxycycline if $\geq$8 years of age (4 mg/kg/day in two divided doses [maximum of 100 mg per dose]) (B-I) is recommended. Oral therapy is easier to administer than IV antibiotics, is associated with fewer serious complications and is considerably less expensive. However, it is important to recognize that a small number of patients treated with oral agents have subsequently manifested overt neuroborreliosis, which may require IV therapy with a beta-lactam antibiotic (see below) for successful resolution. Further controlled trials are needed to compare the safety and efficacy of oral with IV therapy for Lyme arthritis.

Neurologic evaluation that may include lumbar puncture should be performed for patients in whom there is a clinical suspicion of neurologic involvement. Adult patients with arthritis and objective evidence of neurologic disease should receive parenteral therapy with ceftriaxone (A-II) for 2 to 4 weeks. Cefotaxime or penicillin G administered parenterally is an acceptable alternative (B-II). For children, IV ceftriaxone or IV cefotaxime is recommended (B-III); penicillin G administered IV is an alternative (B-III). See above recommendations for treatment of patients with Lyme meningitis for suggested doses of each of these antimicrobials.

For patients who have persistent or recurrent joint swelling after a recommended course of oral antibiotic therapy, the panel members recommend retreatment with another 4-week course of oral antibiotics or with a 2 to 4 week course of ceftriaxone IV (B-III) (for dosages of oral agents see the recommendations for treatment of erythema migrans above and for dosages of parenteral agents see the above recommendations for treatment of Lyme meningitis). A second 4-week course of oral antibiotic therapy is favored by panel members for the patient whose arthritis has substantively improved but has not yet completely resolved, reserving IV antibiotic therapy for those patients whose arthritis failed to improve at all or worsened. Clinicians should consider waiting several months before initiating re-treatment with antimicrobial agents because of the anticipated slow resolution of inflammation after treatment. If patients have no resolution of arthritis despite IV therapy and if polymerase chain reaction (PCR) results on a sample of synovial fluid (and synovial tissue if available) are negative, symptomatic treatment is recommended (B-III). Symptomatic therapy might consist of non-steroidal anti-inflammatory agents, intra-articular injections of corticosteroids, or disease modifying anti-rheumatic drugs (DMARDs) such as hydroxychloroquine; expert consultation with a rheumatologist is recommended.

If persistent synovitis is associated with significant pain or limitation of function, arthroscopic synovectomy may reduce the duration of joint inflammation (B-II).

Late Neurologic Lyme Disease

Adult patients with late neurologic disease affecting the central or peripheral nervous system should be treated with IV ceftriaxone for 2 to 4 weeks (B-II). Cefotaxime or penicillin G administered IV is an alternative (B-II). Response to treatment is usually slow and may be incomplete. Retreatment is not recommended unless relapse is shown by reliable objective measures. Ceftriaxone is also recommended for children with late neurologic Lyme disease (B-II). Cefotaxime or penicillin G administered IV is an alternative (B-III). See above recommendations on the treatment of Lyme meningitis for suggested doses of each of these antimicrobials.

Acrodermatitis Chronica Atrophicans

Available data indicate that acrodermatitis chronica atrophicans may be treated with a 21-day course of the same antibiotics (doxycycline [B-II]; amoxicillin [B-II]; cefuroxime axetil [B-III]) used to treat patients with erythema migrans (see above). A controlled study is warranted to compare oral with parenteral antibiotic therapy for the treatment of acrodermatitis chronica atrophicans.

Coinfection

Coinfection with Babesia microti or Anaplasma phagocytophilum or both may occur in patients with early Lyme disease (usually in patients with erythema migrans) in geographic areas that are endemic for these pathogens. Coinfection should be considered in patients who present with more severe initial symptoms than are commonly observed with Lyme disease alone, especially in those who have high-grade fever for more than 48 hours despite antibiotic therapy appropriate for Lyme disease or who have unexplained leukopenia, thrombocytopenia, or anemia (A-III). Coinfection might also be considered in the situation in which there has been resolution of the erythema migrans skin lesion but either no improvement or worsening of viral infection-like symptoms (B-III).

Post-Lyme Disease Syndromes

There is no well-accepted definition of post-Lyme disease syndrome. This has contributed to confusion and controversy, and to lack of firm data on its incidence, prevalence, and pathogenesis. In an attempt to provide a framework for future research on this subject and to reduce diagnostic ambiguity in study populations, a definition for post-Lyme disease syndrome is proposed in the original guideline document (Table 6). Whatever definition is eventually adopted, having once had objective evidence of B. burgdorferi infection must be a conditio sine qua non. Furthermore, when laboratory testing is done to support the original diagnosis of Lyme disease, it is essential that it be performed by well-qualified and reputable laboratories which use recommended and appropriately validated testing methods and interpretive criteria. Unvalidated test methods (such as urine antigen tests or blood microscopy for borrelia) should not be used.

There is no convincing biologic evidence for the existence of symptomatic chronic B. burgdorferi infection among patients after recommended treatment regimens for Lyme disease. Antibiotic therapy has not proven to be useful and is not recommended for patients with chronic (≥6 months) subjective symptoms after recommended treatment regimens for Lyme disease (E-I).

Therapeutic Modalities Not Recommended

Due to lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient, the following are not recommended for treatment of patients with any manifestation of Lyme disease: first generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine penicillin G, combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not others), long-term antibiotic therapy, anti-bartonella therapies, hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide, specific nutritional supplements, and others (see full text and Table 5 in the original guideline document) (E-III).

Human Granulocytic Anaplasmosis

All symptomatic patients suspected to have HGA should be treated with antimicrobial therapy because of the risk of complications (A-III). Suspicion for HGA is based on the acute onset of unexplained fever, chills and headache, often in association with thrombocytopenia, leukopenia, and/or increased liver enzymes in patients with exposure to I. scapularis or I. pacificus ticks within the prior 3 weeks. Confirmation of the diagnosis is based on laboratory testing (see full text of the original guideline document), but antibiotic therapy should not be delayed in a patient with a suggestive clinical presentation pending the results. Identification of the characteristic intra-granulocytic inclusions on blood smear is the most rapid diagnostic method, but such inclusions are often scant in number or sometimes absent; in addition, other types of inclusions unrelated to HGA or overlying platelets can be misinterpreted by inexperienced observers. Testing for antibody to A. phagocytophilum is the most sensitive diagnostic method but only if a convalescent serum sample is assayed.

Doxycycline is recommended as the treatment of choice for patients who are suspected to have symptomatic HGA (A-II). The dosage regimen for adults is 100 mg given twice daily by mouth (or IV for those patients unable to take an oral medication) for 10 days. This treatment regimen should be adequate therapy for patients with HGA alone and for patients who have coinfection with B. burgdorferi. Persistence of fever for more than 48 hours after initiation of doxycycline suggests that the diagnosis of HGA is incorrect or more remotely that the patient may be coinfected with Ba. microti.

Although a 10 day treatment course of doxycycline may be offered to all children as well (C-III), the panel preferred a modified approach in which severity of illness, age of the child, and the presence or absence of coinfection with B. burgdorferi were each considered in order to minimize an already low risk of drug toxicity. The suggested dosage of doxycycline for children with HGA is 4 mg/kg/day in two divided doses (maximum 100 mg per dose) given orally (or IV

for children unable to take an oral medication). Children at least 8 years of age may be treated with a 10-day course of doxycycline. For severely ill children younger than 8 years of age without concomitant Lyme disease, the panel recommended an abbreviated treatment course of 4 to 5 days, i.e., for approximately 3 days after resolution of fever (B-III). Children treated with an abbreviated course of therapy should be closely observed to ensure resolution of clinical and laboratory abnormalities. If the child has concomitant Lyme disease, then amoxicillin (50 mg/kg/day in three divided doses [maximum of 500 mg per dose]) or cefuroxime axetil (30 mg/kg/day in two divided doses [maximum of 500 mg per dose]) should be initiated at the conclusion of the course of doxycycline to complete a 14 day total course of antibiotic therapy (B-III).

Patients with mild illness due to HGA who are not optimally suited for doxycycline treatment due to a history of drug allergy, pregnancy, or age less than 8 years, may be treated with rifampin for 7 to 10 days using a dosage regimen of 300 mg twice daily by mouth for adults and 10 mg/kg twice daily for children (maximum of 300 mg per dose) (B-III). Rifampin-treated patients should be closely observed to ensure resolution of clinical and laboratory abnormalities. Since rifampin is not effective therapy for Lyme disease, patients coinfected with B. burgdorferi should also be treated with amoxicillin or cefuroxime axetil as used for the treatment of erythema migrans (see above) (A-I). No other antimicrobial can be recommended for the treatment of HGA (E-III).

Treatment is not recommended for asymptomatic individuals who are seropositive for antibodies to A. phagocytophilum (E-III).

Babesiosis

All patients with active babesiosis should be treated with antimicrobial therapy because of the risk of complications (A-III). Diagnostic criteria for active babesial infection should include the presence of viral infection-like symptoms and identification of babesial parasites in blood by smear evaluation or by PCR amplification of babesial DNA. Symptomatic patients whose serum contains antibody to babesia but whose blood lacks identifiable babesial parasites on smear or babesial DNA by PCR should not receive treatment (E-III). Treatment is also not recommended for asymptomatic individuals regardless of the results of serology, blood smears, or PCR (E-III). Asymptomatic patients with positive babesial smears and/or PCR should have these studies repeated and a course of treatment considered if parasitemia persists for more than 3 months (B-III).

The combination of either atovaquone plus azithromycin or clindamycin plus quinine for 7 to 10 days is the initial therapy that should be considered for patients with babesiosis (A-I). Clindamycin and quinine should be given for those with severe babesiosis (A-III). In such patients clindamycin should be administered IV rather than orally and exchange transfusion should be considered. Longer duration of antimicrobial therapy may be necessary in highly and persistently symptomatic patients until parasitemia is cleared, but no controlled studies exist that define the risk/benefit ratio of more prolonged therapy.

The dosage regimen of atovaquone plus azithromycin for adults is atovaquone 750 mg orally every 12 hours and azithromycin 500 to 1,000 mg on day 1 and

250 mg once a day thereafter by the oral route. For immunocompromised patients with babesiosis, higher doses of azithromycin (600 to 1,000 mg per day) may be used. The doses for children are atovaquone 20 mg/kg every 12 hours (up to a maximum of 750 mg per dose) and azithromycin 10 mg/kg/day once per day on day 1 (up to a maximum of 500 mg per dose) and 5 mg/kg/day once per day (up to a maximum of 250 mg per dose) thereafter by the oral route.

The dosage regimen of clindamycin plus quinine for adults is clindamycin 300 to 600 mg every 6 hours IV, or 600 mg every 8 hours orally, and quinine 650 mg every 6 to 8 hours orally. Doses for children are clindamycin 7 to 10 mg/kg given IV or orally every 6 to 8 hours (up to a maximum of 600 mg per dose) and quinine 8 mg/kg given orally every 8 hours (up to a maximum of 650 mg per dose).

Partial or complete red blood cell exchange transfusion is indicated for those with severe babesiosis as indicated by high grade parasitemia ($\geq$10%), significant hemolysis, or renal, hepatic, or pulmonary compromise (A-III). No data are available to determine whether partial exchange transfusion is preferable to whole blood exchange; expert consultation with an infectious diseases expert and a hematologist is recommended.

Patients with moderate to severe babesiosis should be monitored closely during therapy to ensure clinical improvement and improvement of parasitemia and other laboratory abnormalities (A-III). In patients with mild to moderate babesiosis, clinical improvement should occur within 48 hours after antiprotozoal therapy is begun and symptoms should completely resolve within three months of initiation of therapy. In severely ill patients, the hematocrit and percentage of parasitized erythrocytes should be monitored daily or every other day until the patient has improved and the parasitemia has decreased to less than 5%. Some patients may have persistence of low grade parasitemia for months after specific antimicrobial therapy.

Physicians should consider the possibility of coinfection with B. burgdorferi or A. phagocytophilum or both in patients with especially severe or persistent symptoms despite appropriate anti-babesial therapy (A-III). Patients found to have coinfection should be treated with additional antimicrobial therapy as described above. An underlying immune deficiency (including asplenia or prior splenectomy, malignancy, or human immunodeficiency virus [HIV] infection) also should be considered in patients with severe or prolonged episodes of babesiosis.

Retreatment of patients with antibabesial therapy as outlined above should be considered if babesial parasites or amplifiable babesial DNA is detected in blood three or more months after initial therapy regardless of symptom status (A-III). However, such assays need not be done routinely for immunocompetent patients who are asymptomatic.

Definitions of Strength of Recommendation and Quality of Evidence Ratings:

Quality of Evidence

I. Evidence from at least one properly randomized, controlled trial

II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results of uncontrolled experiments
III. Evidence from opinions of respected authorities on the basis of clinical experience, descriptive studies, or reports of expert committees

Strength of Recommendation

A. Strongly in favor
B. Moderately in favor
C. Optional
D. Moderately against
E. Strongly against

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Prevention of transmission of Borrelia burgdorferi, Anaplasma phagocytophilum, and Babesia microti
- Appropriate assessment and treatment of Lyme disease, human granulocytic anaplasmosis, and babesiosis and prevention of late complications

POTENTIAL HARMS

- Adverse effects of antimicrobial therapy
- Drug-induced rashes occur with both amoxicillin and cefuroxime axetil. Doxycycline may cause photosensitivity, which may be problematic since early Lyme disease occurs most commonly during the summer months. Individuals treated with doxycycline are advised to avoid exposure to the sun while on therapy. Doxycycline should be taken with 8 oz of fluid to reduce the risk of esophageal irritation and with food to reduce gastrointestinal intolerance.
- Oral therapy is easier to administer than intravenous antibiotics, is associated with fewer serious complications, and is considerably less expensive. Its disadvantage is that some patients treated with oral agents have subsequently manifested overt neuroborreliosis, which may require intravenous therapy for successful treatment.

CONTRAINDICATIONS

CONTRAINDICATIONS

Doxycycline is relatively contraindicated during pregnancy or lactation, and in children < 8 years of age.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, Krause PJ, Bakken JS, Strle F, Stanek G, Bockenstedt L, Fish D, Dumler JS, Nadelman RB. Infectious Diseases Society of America practice guidelines for clinical assessment, treatment and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis. Alexandria (VA): Infectious Diseases Society of America; 2006 Jun 27. 150 p. [381 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Jul (revised 2006 Jun)

GUIDELINE DEVELOPER(S)

Infectious Diseases Society of America - Medical Specialty Society

SOURCE(S) OF FUNDING

Infectious Diseases Society of America (IDSA)

GUIDELINE COMMITTEE

Infectious Diseases Society of America (IDSA) Standards and Practice Guidelines Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Wormser GP, Nadelman RB, Dattwyler RJ, Dennis DT, Shapiro ED, Steere AC, Rush TJ, Rahn DW, Coyle PK, Persing DH, Fish D, Luft BJ. Practice guidelines for the treatment of Lyme disease. Clin Infect Dis 2000 Jul;31(Suppl 1):1-14.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Infectious Diseases Society (IDSA) Web site.

Print copies: Available from Gary P. Wormser, MD, Room 245, Munger Pavilion, New York Medical College, Valhalla, NY 10595

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Kish MA. Guide to development of practice guidelines. Clinical Infectious Diseases 2001;32:851-4.

Electronic copies: Available from the Clinical Infectious Diseases Web site.

Print copies: Available from Clinical Infectious Diseases, Subscription Fulfillment, P.O. Box 37005, Chicago, IL 60637

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on May 1, 2001. The information was verified by the guideline developer as of June 29, 2001. This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This NGC summary was updated on July 25, 2006. The updated information was verified by the guideline developer on September 7, 2006.

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